بسم الله الرحمن الرحيم

Diabetes Mellitus in Pregnancy: A Clinical and Public Health Problem

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FRCOG, FRCS (Ed), MSc in Assisted Reproduction Technology

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I am grateful to the thousands of patients who have contributed their valuable time, efforts and unconditional support towards my projects. I have learned a lot from them.

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Declaration: I, Dr. Haifa A. A. Wahabi, declare that this thesis is submitted to the University of Warwick in support of my application for the degree of Doctor of Philosophy. It has been composed by myself and has not been submitted in any previous application for any degree. This work was carried out between October 2010 and August 2013.

The work presented (including data generated and data analysis) was carried out by the author and signed by the collaborating authors:

Preconception care for diabetic women for improving maternal and fetal outcomes: a systematic review and meta-analysis

Hayfaa A Wahabi, Rasmeia A Alzeidan, Ghada A Bawazeer, Lubna A Alansari, Samia A Esmaeil

Haifa Wahabi conceived the idea of the review, was responsible for drafting and writing the study protocol and reviewing the search strategy. Haifa Wahabi was responsible, with the other co-authors, for study selection, data extraction, quality assessment of studies and data analysis. She was responsible for writing the final report of the manuscript.

Lubna Alansary ---

Rasmiah Alzeidan --

Gahadah Bawazeer --

Samia Esmaeil --

Pre-pregnancy care for women with pre-gestational diabetes mellitus: a systematic review and meta-analysis

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Rasmiah Alzeidan --
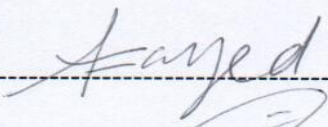
Samia Esmaeil --

Pre-existing diabetes mellitus and adverse pregnancy outcomes

Hayfaa A Wahabi, Samia A Esmaeil, Amel Fayed , Ghadeer Al-Shaikh and Rasmieh A Alzeidan

Haifa Wahabi conceived the idea for the study; she supervised the data collection and analysis and she wrote the final manuscript.

Samia Esmaeil --
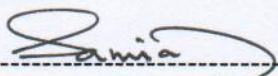
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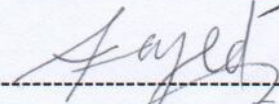
Rasmiah Alzeidan --

Ghadeer Al-Shaikh --

Gestational diabetes mellitus: maternal and perinatal outcomes in KKUH, Saudi Arabia.

Hayfaa A Wahabi, Samia A Esmaeil, Amel Fayed and Rasmieh A Alzeidan

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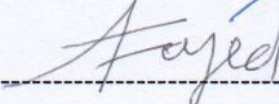
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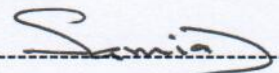
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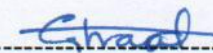
Factors associated with successful induction of labour

Haifa Wahabi supervised the data collection, data analysis and wrote the final manuscript.

Ghadeer K. Al-Shaikh, ---

Amel Fayed ---

Samia Esmaeil ---

Ghada Al-Malki ---

Abbreviations:

DM: Diabetes mellitus

T2DM: Type 2 diabetes mellitus

T1DM: Type 1 diabetes mellitus

Pre-GDM: Pre-gestational diabetes mellitus

GDM: Gestational diabetes mellitus.

C/S: Cesarean section

PCC: Preconception care

IADPSG: International **A**ssociation of **D**iabetes and **P**regnancy **S**tudy **G**roup

IOL: Induction of labour.

King Khalid University Hospital: KKUH

Kingdom of Saudi Arabia: KSA

Word Count 7043

Summary

Diabetes is the most frequently encountered endocrine disorder in pregnancy and is associated with adverse outcomes. Despite the urgent need for interventions to improve the outcomes for pregnancies complicated with diabetes, and the consistent recognition of preconception care as an effective intervention, there has been lack of systematically produced evidence to support it.

My first publication (Preconception Care for Diabetic Women for Improving Maternal and Fetal Outcomes: a Systematic Review and Meta-analysis) was the first systematically produced high level evidence addressing the effectiveness and the safety of all aspects of preconception care. This publication had high impact on practice and research evident by the incorporation of its findings in clinical guidelines and the number of times it was cited in the literature. My second publication (Pre-pregnancy care for women with pre-gestational diabetes mellitus: a systematic review and meta-analysis) was designed for deeper analysis of the safety of preconception care.

The third and the fourth publications addressed the prevalence of pre-gestational and gestational diabetes and the rate of complications associated with diabetes in pregnancy in Saudi Arabia and contributed to the quantification of diabetes in pregnancy as a public health problem in the country. These two publications provided important information, considering that there was paucity of publications about diabetes in pregnancy in Saudi Arabia for more than a decade, and they gave the needed evidence to revise the hospital policy for screening and management of diabetes in pregnancy as well as the implementation of preconception care for women with pre-existing diabetes.

My fifth publication investigated an important clinical intervention for pregnant women with diabetes which is induction of labour. Similar to the second and third publication there was paucity of information about the indications and the determinants of successful induction of labour in Saudi Arabia. This publication was the first to address this important intervention in the practice of obstetrics in general and in the specific management of women with diabetes.

Thus my work in "diabetes in pregnancy as a clinical and public health problem" provided an important evaluation of interventions at the clinical and public health levels and important information for the management of diabetic pregnant women in Saudi Arabia and across the world.

Background:

<u>Epidemiology of pre-gestational and gestational diabetes mellitus worldwide:</u>

Diabetes mellitus (DM) is a global public health problem with expected 300 million diabetics by the year 2030 worldwide [1]. In many areas around the globe including the West as well as many developing and Middle Eastern countries, diabetes has become a major health burden affecting young adults and women in their reproductive age [2,3]. As the burden of the disease increases the management of pregnancies complicated by DM will be part of the daily obstetric practice in many regions of the world.

Pregnancies complicated with pre-gestational diabetes mellitus (pre-GDM) are associated with a high rate of complications compared to the background population; including increased perinatal mortality and congenital malformations [4,5]. A recent systematic review showed that pregnancies complicated by type 2 diabetes mellitus (T2DM) are associated with worse perinatal and neonatal mortality than those complicated by type 1 diabetes mellitus (T1DM) [6]. Studies investigating the influence of ethnicity on the outcome of pregnancies complicated by pre-GDM reported variation in the outcome with different ethnic groups with worse outcome for Asian [7] and Afro-Caribbean mothers compared to Caucasian [8], however this difference might be explained by access to and utilization of preconception and prenatal care [8].

Gestational diabetes mellitus (GDM) "is carbohydrate intolerance that begins or is first recognized during pregnancy" [9]. There is great variation in the prevalence of GDM among different ethnic groups and communities; it ranges from less than 2% to

22% [10]. Epidemiological studies confirmed that the prevalence of GDM is in direct proportion to the prevalence of T2DM [11], in addition women who developed GDM are at increased risk of developing T2DM [12,13]. Obesity, high weight gain during pregnancy, increased parity and advanced maternal age are recognized risk factors for developing GDM [11,14,15]. Similar to pre-GDM, GDM is associated with considerable maternal, fetal and neonatal complications [16,17]. In addition, recent reports confirmed that GDM has long term effects on the mothers and their children including increase risk of developing T2DM, maternal and childhood obesity and cardiovascular disease [18].

Epidemiology of pre-GDM and GDM in Saudi Arabia:

Recent population based studies in Saudi Arabia estimated the prevalence of T2DM to be between 21% to 24% [19], which reflects a fivefold increase in the affected population in just over 20 years [20]. Among the Middle East countries, the Gulf region countries showed the highest prevalence of DM; with the Kingdom of Saudi Arabia (KSA) reported the highest prevalence compared to the other Gulf countries. The rapidly increasing prevalence of T2DM has been attributed to the fast changes in lifestyle, dietary habits, and physical activity of the Saudi community associated with the socio-economic changes and fast urbanization [21]. The World Health Organization predicted that DM prevalence in KSA will increase by 183% over the 20 years following 2003 [22].

Despite the confirmed high prevalence of DM, only few studies addressed the prevalence and the effect of maternal diabetes on pregnancy outcomes in KSA.

Similar to other parts of the world diabetes in pregnancy in KSA is associated with increased maternal age, parity and body mass index [23-25]. Although most of these studies were hospital based, yet they showed that almost one fourth of the women admitted for delivery in one hospital had either GDM or pre-GDM [26,27] with demonstrable adverse pregnancy outcomes when compared to non-diabetic women [26,27], including higher rate of macrosomia, cesarean section delivery (C/S), preterm delivery, perinatal mortality and birth injuries [26-29]. In addition newborns of diabetic mothers had higher rate of admission to intensive care unit and higher rate of metabolic disorders [30]

The reported prevalence of GDM, from the different hospital based studies, ranges between 5-18%, depending on different diagnostic criteria, and that of pre-GDM is 3.7-4.2% [27,28], yet the overall incidence and prevalence of GMD and pre-GDM, or economic burden of these important conditions on the health service provision in KSA, is not known due to lack of population based studies in this area, which reflects negatively on the estimation of impact of any preventive or health promotional programs directed towards reducing the burden of GDM and pre-GDM.

The importance of the published literature as source of information for the policy makers cannot be stressed more keeping in mind that there is no national database for maternity health problems in KSA. There is scarcity of information about the standard of health services provided to diabetic pregnant women in addition to lack of national guidelines for screening and treatment of diabetes during pregnancy.

Fetal, neonatal and maternal complications of diabetes in pregnancy:

The physiological changes of pregnancy cause a state of carbohydrate intolerance. Pregnancy specific hormones such as human placental lactogen and the increased levels of cortisol and prolactin, increase insulin resistance and call for more production of insulin to maintain normal blood glucose level during pregnancy [31]. Such demand is not met in pregnant diabetic women due to the pathology associated with diabetes.

The hyperglycemia in T2DM is due to decreased uptake of glucose by the peripheral tissue together with increased hepatic production, this is secondary to reduced production of insulin from the pancreatic β cells and to increased peripheral resistance to insulin [32,33]. On the other hand the hyperglycemia in T1DM is caused by complete destruction of the β cells of the pancreas due to the interplay of auto-immune, genetic and environmental factors [34-36].

The hyperglycemia in GDM typically appears late in pregnancy, hence the recommended screening time between 24-28 gestation weeks.

Maternal hyperglycemia stimulates fetal hyperinsulinemia with subsequent increase and abnormal fat distribution on the fetus [37]. Recent studies have confirmed that hyperglycemia at levels even lower than that for DM in non-pregnant subjects, is associated with adverse pregnancy outcomes in a linear relationship [38].

The effect of hyperglycemia on the pregnancy outcomes varies with the level of maternal blood glucose and the time during pregnancy with uncontrolled hyperglycemia. Hyperglycemia occurring early in pregnancy and during

organogenesis, as in the case of uncontrolled T1DM and T2DM, is associated with risk of congenital malformations, macrosomia, stillbirth, birth asphyxia and preterm delivery, while the same complications might appear with GDM but less frequent and less severe due to the late occurrence of the hyperglycemia [17,39].

The teratogenicity of pre-GDM has long being recognized [40]. Observational studies indicated an increased risk of congenital abnormalities in pregnancies complicated by GDM [40]; however this observation might be due to the inclusion of women with unrecognized T2DM in the study population.

Uncontrolled maternal hyperglycemia adversely influences fetal weight and growth with resultant macrosomia at moderately elevated levels and intra-uterine growth restriction at very high levels of maternal blood glucose [41]. Macrosomia is associated with significant maternal and perinatal complications including increased rate of C/S, birth asphyxia and perinatal mortality [42].

A recent report confirmed that the rate of both iatrogenic and spontaneous preterm deliveries are increased in mothers who are diabetic compared to the background population [43] nevertheless, premature infants of diabetic mothers do not seem to be at risk of complications more than the preterm infants of non-diabetic mothers [44]. The reason behind the tendency towards delivery by C/S is in great part attributed to the increased rate of macrosomia among women with pre-GDM and GDM, however significant association was found between the risk of C/S delivery in diabetic women and maternal obesity, uncontrolled diabetes and unplanned pregnancy [45]. Recent reports found that with the increase rate of elective C/S there was improvement in the

rate of shoulder dystocia and its associated morbidities [46] as well as of APGAR scores at 5 minutes [47], nevertheless the effectiveness and cost effectiveness of the approach of screening for macrosomia by ultrasound scanning, fetal weight estimation and subsequent delivery by elective C/S was doubted by other investigators [48].

The stillbirth rate among women with pre-GDM is high compared to the background population. Recent review on the causes of perinatal mortality in women with pre-GDM showed that antepartum asphyxia and congenital abnormalities were the leading two causes of stillbirth [41]. Placental angiopathy secondary to uncontrolled maternal hyperglycemia was suggested as an etiology for antenatal asphyxia [41] and peri-conception uncontrolled hyperglycemia as the cause of congenital abnormalities [49].

Prevention and treatment of complications of pre-GDM and GDM:

Despite improved access and quality of antenatal care, women with pre-GDM and their fetuses are at increased risk of developing serious complications compared with the non-diabetic pregnant women [50,51].

Evidence for effectiveness and safety preconception care for women with pre-GDM:

Pre- GDM and the associated maternal hyperglycemia during the time of organogenesis is a known teratogen with detrimental effects on the fetal heart, renal, musculoskeletal and central nervous systems [50,52,53]. Population based studies showed that there is a fivefold increase in the rate of cardiovascular malformations,

and more than twofold increase in the rate of neural tube defects and urinary tract abnormalities in infants of diabetic mothers when compared to the background population [52,53]. Moreover congenital malformations are associated with increased risk of stillbirth and perinatal mortality as they account for almost 50% of all deaths of infants born to mothers with pre-GDM [54,55] . Congenital malformations secondary to maternal diabetes can be prevented, in great part, by optimizing maternal health in the preconception period. Glycemic control is one of the most important aspects of preconception care (PCC) [56]; however other aspects of care such as folic acid supplementation, smoking cessation, screening and treatment of diabetes complications and discontinuing teratogenic medications, are as important for improving maternal and fetal outcomes and might be effective in reducing the rate of congenital malformations to the background level [49,57,58]. The evidence for the effectiveness of PCC for women with pre-GDM, in the form of optimization of blood glucose level, folic acid supplementation, detection and treatment of retinopathy and modification of medication has been consistent since 1982 [59]. However previous studies that addressed PCC are either outdated and limited to selected outcomes of pregnancy [56] or to one center of care [33], which created an urgent need for high level of evidence for this important intervention.

Screening for pre-GDM and GDM:

There were controversies about screening and treatment of GDM [60] as well as about early diagnosis of T2DM in pregnancy, however recent reports proved the importance of universal screening and treatment in communities with high prevalence of GDM and T2DM [61,62]. Following the analysis of the results of the study

hyperglycemia and adverse pregnancy outcome (HAPO) [38], a consensus about diagnosis and screening of hyperglycemia in pregnancy was reached by representatives of 10 international organizations; the **I**nternational **A**ssociation of **D**iabetes and **P**regnancy **S**tudy **G**roup (IADPSG) and the recommendations included the use of 2 hours 75g oral glucose tolerance test (OGTT) for all pregnant women between 24 and 28 week of pregnancy to screen and diagnose GDM. The criteria for diagnosing GDM is based on one or more abnormal value of the following; fasting blood glucose ≥ 5.1 mmol/l, 1 hour ≥10 mmol/l and 2 hours ≥ 8.5 mmol/l [63]. The group also recommended early screening of all pregnant women for T2DM during the first antenatal visit using either fasting blood glucose with a cut-off level ≥7.0 mmol/l or glycosylated hemoglobin A (HbA1c) of ≥ 6.5% [63]. The advantage of the recommendation of the IADPSG over previously suggested criteria for the diagnosis of GDM is that they are linked to the risk of adverse pregnancy outcomes rather than to the diagnosis of diabetes outside pregnancy. Moreover, the recommendations addressed the issue of undiagnosed T2DM first recognized during pregnancy by recommending screening for T2DM at booking visit [63,64]

Following the diagnosis of GDM or pre-GDM, normalization of maternal blood glucose by using nutritional regiments and if needed insulin, is of paramount importance to prevent the complications of GDM and pre-GDM [16]. Based on the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS) and the blood glucose level of non-diabetic pregnant women, the recommendation for the target blood glucose levels during pregnancy are; FBG < 5.3 mmo/l, 1hour post-meal < 7.8 mmol/l and 2hours post-meal < 6.7 mmol/l. Close monitoring of maternal blood

glucose by daily testing of fasting and postprandial levels with monitoring of long term control by HbA1c levels, provide valuable information for adjustment of insulin therapy [65].

Dietary advice and exercise were found to be effective in the prevention of GDM. However, the quality of evidence was low as concluded by a recent systematic review [66].

Management of labour and delivery in women with pre-GDM and GDM:

One of the main concerns in the management of pregnant women with diabetes is the increased risk of stillbirth; [67]. The main etiology of stillbirth in diabetic pregnancy is chronic intra-uterine hypoxia secondary to placental vascular pathology [68]. In addition to close fetal surveillance, induction of labour (IOL) is offered to pregnant women with diabetes to avoid sudden intra-uterine fetal death. Moreover IOL for pregnant diabetic women at 38 gestation weeks was proven to improve other outcomes such as fetal macrosomia and shoulder dystocia without increasing the risk of C/S delivery [69,70]. Despite the frequent use of IOL for the management of pregnant women with diabetes there is paucity of evidence about the safety and determinants for successful IOL in Saudi Arabia.

From the aforementioned summary of the problem of pre-GDM and GDM there were unanswered questions which have international and national impact on these condition and these were:

1. No high grade evidence for the effectiveness of PCC.

2. No clear evidence for the safety of PCC with tight glycemic control.

3. Investigation of the prevalence of pre-GDM and GDM in Saudi Arabia with preliminary studies which form the base for population based studies to evaluate all aspects of pre-GDM and GDM including health service provision.

4. There is paucity of evidence about the determinants of success for a common intervention in the management of diabetic pregnant women which is IOL.

Our first study was designed to investigate the effectiveness of PCC (publication 1). As tight glycemic control is associated with significant risk of hypoglycemia, we designed a second study to incorporate the safety element of the PCC (publication 2). To assess the scale of the problem of pre-GDM in KSA, a third study was designed to investigate the prevalence of pre-GDM and its effects on the pregnancy outcomes, in a real life setting (publication 3). Similarly, a separate study was conducted to investigate the prevalence of GDM and its effects (publication 4). Finally, induction of labour is a common mode of delivery intervention in both pre-GDM and GDM, however, real life data on the outcomes of induction of labour is not known in KSA. It is conceivable with increasing number of induction of labour, failure of induction can happen more often resulting in potentially more adverse perinatal outcomes including emergency C/S. Hence we designed an exploratory observational study to assess the indications of IOL and the factors associated with successful IOL (publication 5).

Published article 1[49]

Preconception Care for Diabetic Women for Improving Maternal and Fetal Outcomes: a Systematic Review and Meta-analysis

Introduction:

Despite improved access and quality of antenatal care, women with pre-gestational diabetes and their fetuses are at increased risk of developing serious complications compared with the non-diabetic pregnant women, including spontaneous abortion, preterm labour, hypertensive disorders, congenital malformations, delivery by C/S and increased perinatal mortality rate [50,51]. In the recent report of The Confidential Inquiry into Maternal and Child Health (CEMACH) from England, Wales and Northern Ireland, the perinatal mortality for mothers with T1DM and T2DM was four times higher and the congenital malformations were twice as much as the background population [50]. Similar reports from North America showed no significant improvement in fetal and neonatal outcomes of women with pre-GDM between 1988 and 2002 [71] despite the Saint Vincent Declaration in 1989 which sets a healthcare goal to improve the outcome of pregnancies in diabetic women [72]. Similar reports from the Middle East showed higher rate of perinatal mortality in diabetic as compared to non-diabetic women [73].

Many of the complications of pre-GDM during pregnancy can be prevented by optimizing maternal health in the preconception period. Glycemic control is one of the most important aspects of PCC [56,57] ; however other aspects such as folic acid supplementation, smoking cessation, screening and treatment of diabetes

complications and discontinuing teratogenic medication, are as important for improving maternal and fetal outcomes [57].

We carried out this systematic review to assess the effectiveness and safety of PCC in improving maternal and fetal outcomes for women with T1DM and T2DM and to provide high level of evidence to guide practice and policy in the management of women with pre-GDM.

Methods:

We searched the following databases, MEDLINE, EMBASE, WEB OF SCIENCE, Cochrane Library, including the CENTRAL register of controlled trials and CINHAL up to December 2009, without language restriction, for any preconception care aiming at health promotion, glycemic control and screening and treatment of diabetes complications in women of reproductive age group with type I or type II diabetes. Study design were trials (randomized and non-randomized), cohort and case-control studies. Of the 1612 title scanned 44 full papers were retrieved of those 24 were included in this review. Twelve cohort studies at low and medium risk of bias, with 2502 women, were included in the meta-analysis.

Results:

Meta-analysis suggested that preconception care is effective in reducing congenital malformation, RR 0.25 (95% CI 0.15-0.42), NNT17 (95% CI 14-24), preterm delivery, RR 0.70 (95% CI 0.55-0.90), NNT= 8 (95% CI 5-23) and perinatal mortality RR 0.35 (95% CI 0.15-0.82), NNT= 32 (95% CI 19-109). Preconception care lowers HbA1c in the first trimester of pregnancy by an average of 2.43% (95%

CI 2.27-2.58). Women who received preconception care booked earlier for antenatal care by an average of 1.32 weeks (95% CI 1.23-1.40).

The effectiveness of preconception care in improving maternal and fetal outcomes

Figure (1): Risk ratio for congenital malformations from 11 studies of women with preexisting diabetes mellitus who did or did not receive preconception care.
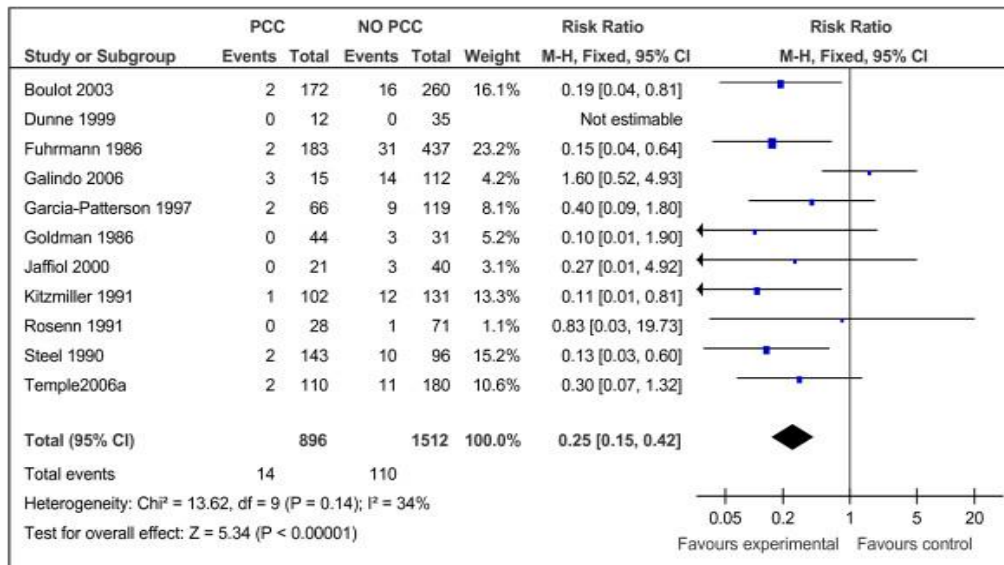
PCC= the group who received preconception care; NPCC= the group who did not received preconception care; CI= Confidence intervals.

Figure (2): Risk ratio for preterm delivery from 4 studies of women with preexisting diabetes mellitus who did or did not receive preconception care.

Study or Subgroup	Preconception care Events	Total	no preconception care Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Dunne 1999	5	12	15	35	6.9%	0.97 [0.45, 2.10]
Garcia 1997	15	66	29	119	18.7%	0.93 [0.54, 1.61]
Jaffiol 2000	7	21	24	40	14.9%	0.56 [0.29, 1.07]
Temple 2006 a	34	110	87	180	59.5%	0.64 [0.47, 0.88]
Total (95% CI)		209		374	100.0%	0.70 [0.55, 0.90]
Total events	61		155			

Heterogeneity: Chi² = 2.55, df = 3 (P = 0.47); I² = 0%
Test for overall effect: Z = 2.86 (P = 0.004)
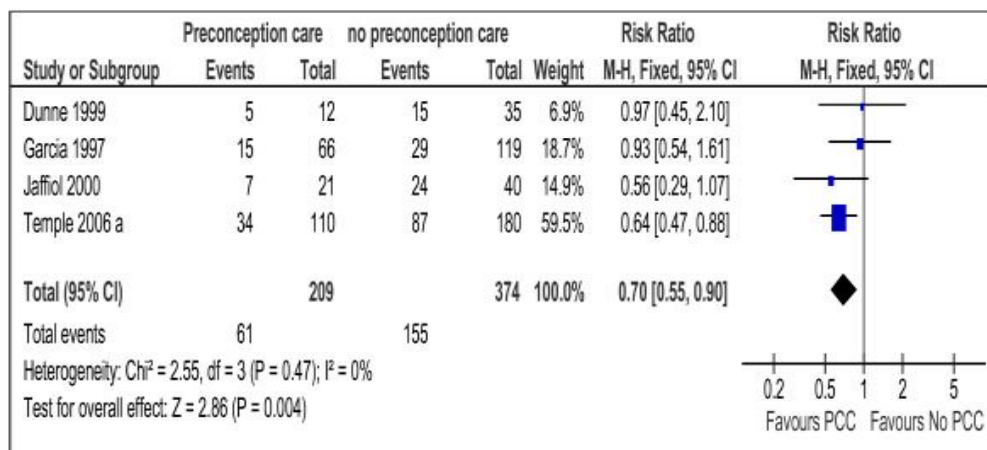
PCC= Preconception care; NPCC= No preconception care; CI= Confidence intervals.

Figure (3): Risk ratio for perinatal mortality from 5 studies of women with preexisting diabetes mellitus who did or did not receive preconception care.
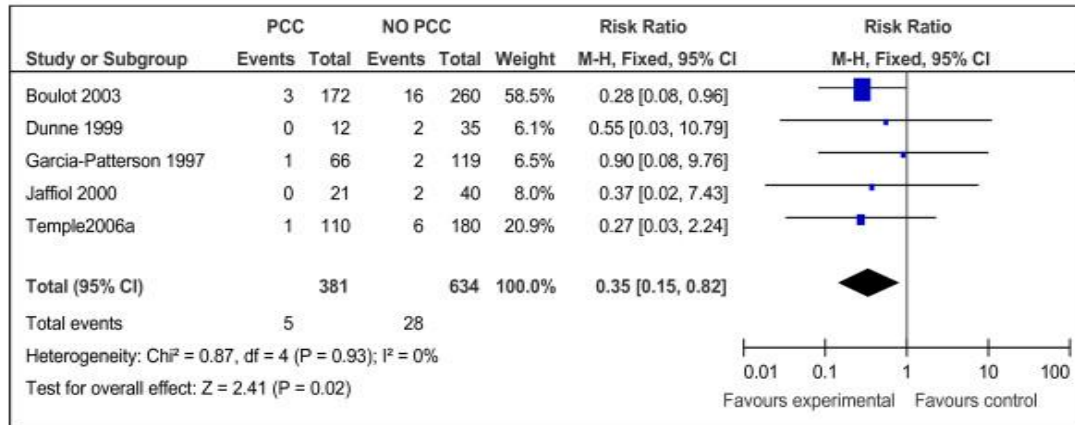
PCC= the group who received preconception care; NPCC= the group who did not received preconception care; CI= Confidence intervals.

Summary and significance of publication 1:

This systematic review provided high level evidence for the effectiveness of PCC in improving many of the maternal and neonatal complications associated with pre-GDM. It is the first systematic review addressing the effectiveness of PCC since the last systematic review was published by Ray et al in 2001[56].

PCC reduced congenital malformations by 75%. This remarkable reduction in the prevalence of congenital malformations has practical implications for many communities worldwide, where congenital malformations due to diabetes and other causes, constitute a major health problem [50,74,75].

The meta-analysis from this systematic review proved that women who attended PCC had 30% reduction in the rate of preterm delivery compared to women who did not.

The effect of PCC in reducing the rate of congenital malformations and preterm deliveries reflected positively on its effect in reducing the perinatal mortality among women who utilized the care with reduction of 65% in perinatal mortality rate compared to women who did not attend PCC. A population based study showed that; in women with pre-GDM, 16-28% of perinatal mortality is due to congenital malformations, and an additional 21-41% is due to preterm delivery [76,77]. Since the rate of both complications improves with PCC, such major reduction in perinatal mortality is expected in women attending PCC.

The strength of this review comes from the comprehensive evaluation of the available evidence on the effectiveness and safety of PCC together with the assessment of wide range of interventions which we considered as PCC and all the possible maternal, fetal and neonatal outcomes which are affected by maternal pre-GDM. We are aware of the limitations of the observational studies as the main source of evidence and the inherent bias associated with the design; however, randomized controlled trials to assess the effectiveness of PCC are neither ethical nor feasible. Nevertheless the nature of the intervention lent strength to the observational studies by avoiding certain biases known to occur in such study designs. Lack of allocation concealment and blinding of participants were avoided by recruiting the intervention and the control groups at different times during the course of the study (preconception period and antenatal period). Additionally, and due to the relatively short duration of the pregnancy, attrition bias was minimized.

The review carries important implications for practice and research as it highlights the importance of the integration of PCC in the routine care of diabetic women during

their reproductive age, and have practical implication considering the many reports worldwide which showed that women with pre-GDM have worse pregnancy outcomes compared to non-diabetic women despite improved access and utilization of antenatal and intra-partum care [50]. One of the main obstacles to the full implementation of PCC programs is the failure of the target population to utilize the provided services [58]. We suggest that more research is needed in methods of encouraging diabetic women to utilize PCC.

This systematic review was cited by 45 articles, books and documents including a World Health Organization's document on the prevention of non-communicable diseases and promotion of maternal health [78]. In addition the review was the main evidence for the recommendation for implementation of PCC in the management of women with pre-GDM in international guidelines; Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada [79]. The review was included in Database of Abstract of Reviews of Effectiveness (DARE) as it meets the quality criteria set by York Center for Review and Dissemination.

Published article 2 [80]

Pre-pregnancy care for women with pre-gestational diabetes mellitus: a systematic review and meta-analysis

Introduction:

Following the publication of additional articles on PCC [58,81] [82] [83] we felt the need to update our published systematic review to incorporate new evidence about safety of PCC thus we designed a second systematic review which resulted in this publication.

Methods:

We searched the following databases, MEDLINE, EMBASE, WEB OF SCIENCE, Cochrane Library, including the CENTRAL register of controlled trials and CINHAL up to December 2011, without language restriction, for any preconception care aiming at health promotion, glycemic control and screening and treatment of diabetes complications in women with type I or type II diabetes. Study design were trials (randomized and non-randomized), cohort and case-control studies.

Results:

Of the 2452 title scanned 54 full papers were retrieved of those 21 studies were included in this review. Twelve cohort studies at low and medium risk of bias, with 3088 women, were included in the meta-analysis. Meta-analysis suggested that preconception care is effective in reducing congenital malformation, RR 0.25 (95% CI 0.16-0.37), NNT19 (95% CI 14-24), and perinatal mortality RR 0.34 (95% CI 0.15-0.75), NNT= 46 (95% CI 28-115). Preconception care lowers HbA1c in the first

trimester of pregnancy by an average of 1.92% (95% CI -2.05 to -1.79). However women who received preconception care were at increased risk of hypoglycemia during the first trimester of pregnancy RR 1.51 (95% CI 1.15-1.99).

The effectiveness and safety of preconception care in improving maternal and fetal outcomes

Figure (4): First trimester mean value of glycosylated hemoglobin A1C from five studies of women with pre-gestational diabetes mellitus who did or did not receive pre-pregnancy care.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Evers 2004	6.4	0.9	271	7	1.4	152	27.7%	-0.60 [-0.85, -0.35]
Glodman 1986	7.38	0.34	44	10.42	0.47	31	45.0%	-3.04 [-3.23, -2.85]
Rosenn 1991	8.5	1.2	28	10	2.7	71	2.9%	-1.50 [-2.27, -0.73]
Steel 1990	8.5	1.3	143	10.5	2	96	8.2%	-2.00 [-2.45, -1.55]
Temple 2006a	6.5	1.1	110	7.6	1.7	180	16.2%	-1.10 [-1.42, -0.78]
Total (95% CI)			596			530	100.0%	-1.92 [-2.05, -1.79]

Heterogeneity: Chi² = 264.43, df = 4 (P < 0.00001); I² = 98%
Test for overall effect: Z = 28.98 (P < 0.00001)

Mean Difference IV, Fixed, 95% CI

-100   -50   0   50   100
Favours experimental   Favours control

PPC (experimental) = the group who received pre-pregnancy care; NPPC (control) = the group who did not received pre-pregnancy care; CI = Confidence intervals.

Figure (5): Risk ratio of maternal hypoglycemia from two studies of women with preexisting diabetes mellitus who did or did not receive preconception care.
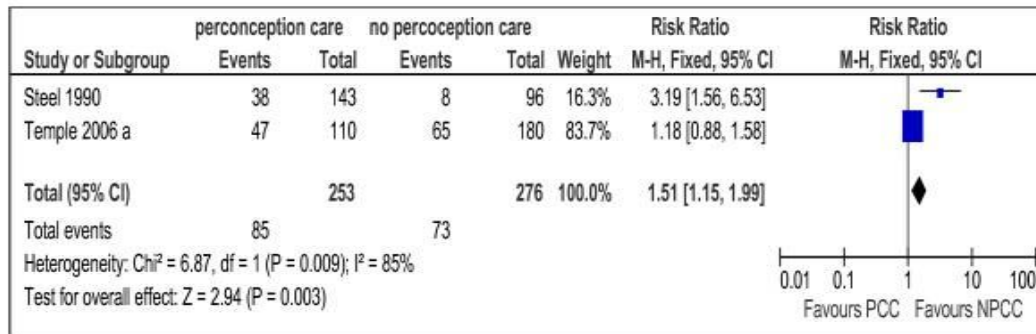
PCC= the group who received preconception care; NPCC= the group who did not received preconception care; CI= Confidence intervals.

Summary and significance of publication 2:

This publication confirmed the findings of the first systematic review on the effectiveness of PCC on reducing the rate of congenital malformations, perinatal mortality, and the level of hemoglobin A1C in the first trimester of pregnancy in diabetic women who utilized PCC compared to those who did not. It also confirmed the previous findings of early utilization of antenatal care by women who had PCC compared to those who did not by nearly two weeks. However this systematic review provided stronger evidence due to the inclusion of 900 women more over the previous review in the meta-analysis in addition to the detailed explanation of the statistical heterogeneity noted in the meta-analysis of the effect of PCC on reducing hemoglobin A1C in the first trimester with the conclusion that the heterogeneity was in the magnitude of the reduction in hemoglobin A1C rather than in the direction of its effect. The other important heterogeneity was that associated with the occurrence of more attacks of severe hypoglycemia in women who utilized PCC compared to

women who did not. This statistical heterogeneity was explained by the variable effect size of PCC on maternal hypoglycemia in the two studies included in the meta-analysis (see figure above). And this variable effect is due to the 16 year interval between the two studies and the many innovations in the treatment of diabetes in pregnancy such as patients' education and counseling, intensive self-monitoring of blood glucose and functional insulin therapy. The conclusion from the analysis was that although meta-analysis suggested an increased risk of severe hypoglycemia with PCC, we believe this is an unlikely adverse effect with modern treatment and monitoring of diabetes during pregnancy.

During the year and a half since this review was published it was cited by 7 articles and has been included in the DARE as it meets the quality criteria set by York Center for Review and Dissemination.

Published article 3 [26]

Pre-existing diabetes mellitus and adverse pregnancy outcomes

Introduction:

Following the publication of our first systematic review and as part of our mission of transferring evidence into practice, we designed a strategy for knowledge translation of PCC to be integrated into the health services provision in KSA taking KKUH as a practical example. As the first step of the **knowledge to action framework** proposed by Graham et al is identification of the problem [84], we needed information about the prevalence of pre-GDM among the pregnant population and its effects on the pregnancy outcomes.

Since there is no national database for maternal diseases in KSA and the few published hospital based studies were more than a decade old, there was paucity of information about the prevalence of pre-GDM and its effects on the outcomes of pregnancy especially that the prevalence of T2DM has risen dramatically in the Saudi community, we designed this study to provide the necessary evidence to evaluate the problem of pre-GDM and its effect in the pregnancy outcome in the hospital.

Methods:

This was a retrospective cohort study for women who delivered in KKUH during the period of January 1st to the 31st of December 2008. The pregnancy outcomes of the women with pre-GDM were compared to the outcomes of all non-diabetic women who delivered during the same study period. Data compared included; age, parity, mode of delivery, premature delivery at less than 37 weeks of gestation, previous

history of miscarriage, birth weight, macrosomia, rate of APGAR scores less than 7 at five minutes and rate of stillbirth. Student *t* test was used to compare continuous variables and Chi square was used to compare categorical variables. Outcomes for macrosomia and mode of delivery were adjusted for maternal age and parity using regression analysis.

Results:

A total of 3157 deliveries met the inclusion criteria. Out of the study population 116 (3.7%) women had pre-GDM. There were 66 (57%) women with T1DM and 50 (43%) women with T2DM. Compared to non-diabetic women those with pre-GDM were significantly older, of higher parity and they had more previous miscarriages. Women with pre-GDM were more likely to be delivered by emergency C/S, OR 2.67, 95% confidence intervals (CI) (1.63-4.32), p < 0.001, or elective C/S, OR 6.73, 95% CI (3.99-11.31), p < 0.001. The neonates of the mothers with pre-GDM were significantly heavier, p < 0.001; and more frequently macrosomic; OR 3.97, 95% CI (2.03-7.65), p 0.002. They more frequently have APGAR scores <7 in 5 minutes, OR 2.61, 95% CI (0.89-7.05), p 0.057 and more likely to be delivered at <37 gestation weeks, OR 2.24, 95% CI (1.37- 3.67), p 0.003. The stillbirth rate was 2.6 times more among the women with pre-GDM; however the difference did not reach statistical significance, p 0.084.

Summary and significance of publication 3:

The results of this study were pivotal for further planning for implementation of PCC. The prevalence of pre-GDM in this study was 3.7% which indicates a fivefold

increase during the last 14 years based on earlier studies from Saudi Arabia [39,85]. The results proved that almost 4 of every 100 women who deliver in the hospital has pre-GDM in addition to 18 women who develop GDM during the course of their pregnancy with the result that almost 25% of the women who deliver in the hospital are at increased risk of adverse maternal and perinatal outcomes. Moreover the study showed that 50% of women with pre-GDM were delivered by C/S compared to less than 20% C/S rate among non-diabetics. While only 3% of infants of non-diabetic mothers were macrosomic, 11% of infants of diabetic mothers were macrosomic. The study proved that diabetic mothers were at increased risk of preterm delivery and delivery of stillbirth.

Because early screening of pregnant women for pre-GDM during the first trimester of pregnancy was not in the antenatal care protocol of the maternity unit in KKUH, it is plausible to assume that a proportion of women, who were diagnosed with GDM, later in pregnancy during screening, had undiagnosed T2DM. These results reflect both a major clinical and public health problem considering the high prevalence of diabetes in pregnancy in this sample.

The results of this study were communicated to the head of the department of obstetrics and gynecology at KKUH in written form with the following recommendations:

1. Because of the documented high prevalence of T2DM in the Saudi population we recommend that all pregnant women be screened early in pregnancy

(during the first trimester) using fasting blood glucose to identify women with pre-GDM.

2. Close monitoring and adjustment of insulin therapy based on daily self-monitoring of blood glucose with clear target of blood glucose level values for fasting and postprandial and periodically assessed hemoglobin A1C levels, is imperative for improving the outcomes for women with pre-GDM.

3. The integration of PCC in the health service provision for women in the reproductive age with pre-GDM.

In addition the results of this study were presented during a one-day seminar in knowledge translation for which officials from the Saudi Ministry of Health and members of obstetrics and gynecology departments in teaching and other governmental hospitals were invited.

Since publication this article was cited by 9 other articles.

Published article 4 [27]

Gestational diabetes mellitus: maternal and perinatal outcomes in King Khalid University Hospital, Saudi Arabia

Introduction:

Based on the results of the aforementioned study about the pre-existing diabetes and pregnancy outcomes, and due to the high prevalence of GDM detected in that study compared to previous studies from KSA [39], this study was designed to provide updated data about the prevalence of GDM and the outcomes of pregnancies in women who develop GDM in KKUH.

Methods:

This is a retrospective cohort study investigating the maternal and the neonatal outcomes of women with GDM who delivered in KKUH as compared with the outcomes of non-diabetic women who delivered during the same period. The data were collected from the 1st of January to the 31st of December 2010 from the labour ward registry. The pregnancy outcomes of the women with GDM were compared with the outcomes of non-diabetic women who delivered during the same study period. Data compared included; age, parity, mode of delivery, premature delivery at less than 37 weeks of gestation, birth weight, macrosomia, rate of APGAR scores less than 7 at 5 minutes and rate of stillbirth. Data were analyzed using the statistical package for the social sciences, version 17 (SPSS Inc., Chicago, Illinois, USA). Means were compared using the Student t-test or one-way analysis of variance, as appropriate, and categorical variables were compared using Chi square or Fisher

exact test, as appropriate. P value and odds ratio (OR) were calculated to test for significant differences between the groups. Outcomes for macrosomia and mode of delivery were adjusted for maternal age and parity using regression analysis. Differences at P < 0.05 were considered significant.

Results:

Out of 3041 women who delivered during the study period, 569 (18.7%) had GDM and 2472 (81.3%) were not diabetic. Compared with the non-diabetic women, women with GDM were more likely to be delivered by emergency C/S, odds ratio (OR) 1.30, 95% confidence intervals (CI) (1.02–1.66), or elective C/S (OR 1.72, 95% CI 1.22–2.44, p<0.001). The neonates of the mothers with GDM were significantly heavier and more frequently macrosomic (OR 1.75, 95% CI, 1.14–2.71, p<0.001). There was no significant difference between the two groups in the frequency of APGAR scores less than 7 in 5 min, preterm delivery at less than 37 weeks of gestation, or in the frequency of intrauterine fetal death.

Summary and significance of publication 4:

This study confirmed our previous findings of the high prevalence of nearly 19% of GDM in the studied population. This prevalence is among the highest reported in the region and world [10,17]. Moreover the results confirmed that women with GDM were disadvantaged by worse pregnancy outcomes compared to the non-diabetic women; including a significantly higher rate of C/S delivery and a higher rate of macrosomia. The results of this study gave indications to the inclusion of women with undiagnosed T2DM in the cohort, such as the increased frequency of previous

miscarriage in the women with GDM compared to the non-diabetic women. However the pregnancy outcomes of women with GDM were better compared to the women with pre-GDM from the previous study evident by similar prevalence of preterm delivery and stillbirth to that of the non-diabetic women.

Table (1): The maternal and neonatal outcomes of women with gestational diabetes mellitus and non-diabetic women.

Characteristic	Non-diabetic	Gestational Diabetes Mellitus	OR (95%CI)	P value
	2472 (81.3%)	**569 (18.7%)**		
Emergency C/S	340 (13.8%)	98 (17.3%)	1.37 (1.07-1.76)	< 0.001
Elective C/S	125 (5.1%)	48(8.5%)	1.83 (1.29-2.59)	< 0.001
APGAR scores at 5 minutes <7	42 (1.7%)	6 (1.1%)	0.62 (0.26-1.46)	0.269
Birth weight	3120.14 ±578.18	3197.60 ± 556.67		< 0.001
Macrsomia	76 (3.1%)	30 (5.3%)	1.76 (1.14- 2.71)	0.010
IUFD	32 (1.3%)	5 (0.9%)	0.68 (0.26-1.75)	0.419
Delivery < 37 weeks	222 (9%)	48 (8.5%)	0.94 (0.68- 1.29)	0.696

OR= Odds Ratio, CI= Confidence intervals, C/S= Cesarean section, IUFD= Intra-uterine fetal death,

The results of this study were communicated to the head of the department of obstetrics and gynecology at KKUH in written form with the following recommendations:

1. The results of this study suggested a high prevalence of GDM among the women attending KKUH for antenatal care and delivery, hence we suggest a policy of universal screening rather than risk factor based screening for GDM.

2. Early screening of pregnant women, during the first trimester, for undiagnosed T2DM will facilitate early detection and control and hence better outcome for this category of pregnant women.

3. The obstetrics and gynecology department in the University Hospital should take the lead for development of national guidelines for the management of GDM in KSA in light of the recent evidence.

Published article 5 [86]:

Factors associated with successful induction of labour

Introduction:

Following the evaluation of the screening protocols for pre-GDM and GDM in the hospital and the outcomes of pregnancies complicated with maternal diabetes, in publications 3 and 4, we designed this study to evaluate an important clinical intervention commonly offered to pregnant women with pre-GDM and GDM which is IOL.

Induction of labour is iatrogenic termination of pregnancy before the onset of spontaneous labour. It is frequently used to avoid serious complications to the mother or the fetus, arising from conditions such as; pre-eclampsia, maternal diabetes, intrauterine growth restriction and post-term pregnancy. Nevertheless, IOL may result in undesirable effects, such as increased rate of C/S, post-partum hemorrhage and fetal distress; therefore, it should only be considered when the benefits to the mother and her fetus outweigh the risks of waiting for spontaneous onset of labour.

One of the main concerns in the management of pregnant women with diabetes is the increased risk of stillbirth; this was demonstrated by our third publication where the stillbirth rate in diabetic mothers was more than twofold higher in mothers with diabetes than the non-diabetic. This result is consistent with the findings of other reviewers [67]. The main etiology of stillbirth in diabetic pregnancy is thought to be chronic intra-uterine hypoxia. This was evident by the increased level of amniotic fluid erythropoietin and the depleted iron store in the fetal liver as a result of increased production of fetal hemoglobin to face the increased need for oxygen [68].

In addition to close fetal surveillance, IOL is offered to pregnant women with diabetes to avoid sudden intrauterine fetal death. Moreover IOL for pregnant diabetic women at 38 gestation weeks was proven to improve other outcomes such as fetal macrosomia and shoulder dystocia without increasing the risk of C/S delivery [69,70]

Methods:

This study is a hospital based prospective cohort study of obstetric patients booked for IOL at the Obstetrics and Gynecology Department at KKUH, from April 2010 to March 2011. All women booked for IOL during the study period were included. Successful IOL was defined as achieving vaginal delivery. To assess the general characteristics of the women and their pregnancies as predictors of outcome of IOL, data from women who had successful IOL were compared to the women who were delivered by C/S, these characteristics included; maternal age, body mass index (BMI), parity, gestation age at IOL, indication for IOL, method of IOL, Bishop score at the commencement of IOL and birth weight. Other outcomes investigated included APGAR score at one and five minutes after delivery. The characteristics of women who had successful IOL were compared to those who delivered by C/S. To assess complication rate associated with IOL, we compared the prevalence of postpartum hemorrhage and ruptured uterus between the women who had IOL and women who had spontaneous labour. Data were analyzed using the Statistical Package for Social Sciences version 17 (SPSS Inc., Chicago, IL, USA). Means were compared using the Student t-test and Chi square test was used to compare categorical variables. A $p<0.05$ was considered significant. Crude odds ratio (OR) and their respective 95%

confidence intervals (95% CI) were estimated, adjusted ORs were calculated using multiple logistic regression models.

Results:

The total number of deliveries during the study period was 3522, of which 564 underwent IOL. The prevalence of IOL was 16%. Vaginal delivery was achieved in 472 (84%) women. The most common indications for IOL were post-term pregnancy in 174 (31%), and diabetes mellitus in 131 (23.2%) of the participants. Maternal characteristics associated with risk of C/S were; nulliparity, odds ratio (OR) 1.58; 95% confidence interval (CI) 1.09-2.320; p=0.01, and high maternal BMI (p=0.01). Neonates of women with successful IOL had significantly higher APGAR scores (p=0.04), and more frequent pH ≥7.1 at delivery (p=0.02). There was no difference in the rate of post-partum hemorrhage, C/S, or ruptured uterus between the women who had IOL and those who went into spontaneous labour.

Summary and significance of publication 5:

This study was the first to investigate the intervention of IOL in KSA. The study proved that, in KKUH, diabetes in pregnancy is one of the main indications for IOL, which reflects the high prevalence of pre-GDM and GDM in the studied population. However despite the large number of diabetic women in this cohort, the rate of IOL of 16% is relatively low compared to that of the West of 33% [87,88]. This can be explained by the policy of the obstetric department which restricts IOL to medical indications and excludes elective IOL from its protocol.

The high success rate of IOL of 84% is comparable to that reported by others who

reported similar policy of using cervical ripening before IOL [88].

Table 2 Maternal and Fetal Characteristics associated with successful induction of labour

Characteristics	Women who had vaginal delivery 472 (84%) No (%)*	Women who delivered by cesarean section 92 (16%) No (%)*	OR (95% CI)	P value
Maternal age				
≤ 35 years	328 (74.4)	62 (72.9)	1.07 (0.64-1.8)	0.78
Nullipara	183 (38.6)	47 (52.2)	1.58 (1.09-2.32)	**0.01**
Gestation age (week) 37+	384 (83.5)	68 (79.1)	0.79 (0.49-1.25)	0.32
Post term > 41 weeks	140 (30.4)	31(36.0)	1.25(0.78-2.02)	0.35
Maternal diabetes as indication for IOL	114 (24.1)	17 (18.9)	0.735(0.41-1.29)	0.28

BMI (kg/m^2) (mean ± SD)	32.56 ± 6.09	34.22 ± 6.05		**0.01**
Bishop score < 5	325 (68.7)	67 (74.4)	1.32 (0.79-2.21)	0.31
Cervical dilatation <2 cm	349 (75.2)	72 (80.9)	1.39 (0.79-2.47)	0.25
Birth weight <2500g	57 (12.2)	17 (18.9)	1.68 (0.88-3.15)	0.09
Birth weight ≥4000g	24 (5.1)	7 (7.8)	1.55 (0.59-3.95)	0.33

BMI= Body mass index

*The difference in percentages is due to missing data

Figure (6): Indications for induction of labour
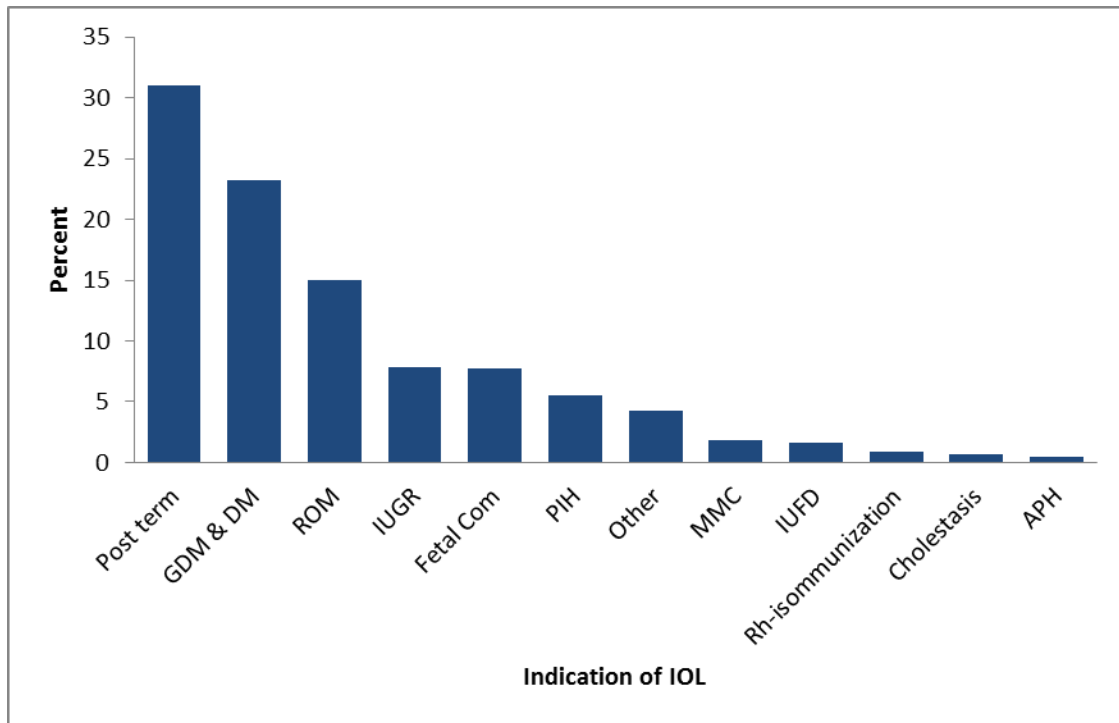
GDM=Gestational diabetes, DM=Diabetes Mellitus, ROM=Rupture of Membranes, IUGR=Intra-uterine growth restriction, Fetal com= Fetal compromise, PIH= Pregnancy induced hypertension, MMC= Maternal Medical Condition, IUFD = Intrauterine Fetal Death, ISO immunization= Rhesus iso-immunization, APH= Ante-partum hemorrhage, IOL = Induction of labour

Future directions and implications of the publications:

Preconception or in-between pregnancy care is a contemporary shift in the paradigm of management of women in the reproductive age. The importance of planning pregnancy and implementing interventions to prevent detrimental effects of pre-existing maternal conditions and behaviors, such as obesity, smoking and uncontrolled hyperglycemia of T1DM and T2DM, on the pregnancy outcomes is no longer disputed [49,89,90]. However it is increasingly recognized that utilization of such care by women is hindered by the high number of unplanned pregnancies and other psychosocial factors [91]. As we recommended in our reports of the systematic reviews, the future direction for PCC, should focus on investigating the barriers for utilization and the incorporation of PCC into the daily health services of women with chronic health conditions such as DM.

Our studies on pre-GDM and GDM had major impact on the practice in the obstetric department of KKUH; mainly through implementation of new clinical practice guidelines based on the recommendation of the IADPSG and universal screening for pre-GDM and GDM.

Based on the results of our studies which demonstrated that mothers with pre-GDM and GDM are at increased risk of adverse pregnancy outcomes and our awareness of the lack of national database for pregnancy complications; we planned and started a multicenter cohort study under the title **Riyadh Birth Cohort** (RBC). This study is expected to provide data pivotal for maternal health policy planning in addition to the opportunity to conduct many longitudinal studies on the mothers and their offspring.

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Appendix 1

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